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DOCKET NO. 17224 (AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
John Sefton

Serial No: 09/367,712; Conf. No. 4667

Filed: August 18, 1999

For: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

Group No. 1616

Examiner: Barbara P. Badio, Ph.D.

CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. §1.10

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service on **March 26, 2004** in an envelope as "Express Mail Post Office To Addressee" mailing label number **EV193720985US** with sufficient postage for Express Mail addressed to Mail Stop Apeal Brief - Patents, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Susan Bartholomew

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Date: March 26, 2004

TRANSMITTAL LETTER FOR BRIEF ON APPEAL

Mail Stop: Appeal Brief-Patents
Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Transmitted herewith is a Brief on Appeal under 37 CFR § 1.1.192(a) in the above-identified application. Enclosed are:

1) Transmittal Letter (1 pg.)
2) Brief on Appeal (8 pgs., in triplicate)
3) Return/Stamped Postcard

Applicant respectfully petitions for a one month extension of time to respond to the final rejection herein under 37 CFR § 1.136 (a).

Please charge our Deposit Account No. 01-0885 in the amount of $440.00. The Commissioner is hereby authorized to charge payment of any additional fees required or credit any overpayment, to Deposit Account No. 01-0885. A duplicate of this sheet is enclosed for that purpose.

Date: March 26, 2004

Respectfully submitted,

Brent A. Johnson

Brent A. Johnson, Ph.D.
Registration No. 51,851
Agent of Record
Telephone: 714-246-4348
Fax: 714-246-4249

DOCKET NO. 17224(AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of
Sefton

Serial No: 09/367,712

Filed: August 18, 1999

For: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

Group Art Unit: 1616
Examiner: Badio, B

Honorable Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Dear Sir:

This appeal is taken from the final rejection of all of the claims in an Examiner's action mailed December 3, 2003. Oral hearing is waived.

(1) REAL PARTY IN INTEREST

This patent application is assigned to Allergan, Inc, having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612.

The application was originally assigned to Allergan Sales, Inc. via an assignment document recorded at Reel/Frame 011144/0193 on August 22, 2000.

Allergan Sales, Inc. (merged into Allergan Sales LLC 6/3/2002) assigned the application to Allergan, Inc. via an assignment document recorded at Reel/Frame 013898/0170 on April 7, 2003.

(2) RELATED APPEALS AND INTERFERENCES

Notice of Appeal was previously filed on October 20, 2000. A new ground of rejection was issued in the Decision on Appeal by the Board on September 24, 2003.

(3) STATUS OF CLAIMS

Claims	Status
1-3	Rejected under 35 USC § 103 as being obvious
4-5	Cancelled
6-8	Rejected under 35 USC § 103 as being obvious
9	Cancelled
10-11	Rejected under 35 USC § 103 as being obvious
12-13	Cancelled

(4) STATUS OF AMENDMENTS

A response after final rejection was filed and considered, but not found persuasive by Examiner.

(5) SUMMARY OF THE INVENTION

The broadest claim at issue provides a method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a high-potency corticosteroid.

(6) ISSUES

Obviousness

In the previous appeal, the Board designated the rejection of Claims 1-3, 6-8, 10 and 11 under 35 USC 103(a) over Yamamoto ('906) and Nagpal ('279) in combination as a new ground of rejection. In response, Applicant's amended claims such that the

remaining scope of the claims has unexpected benefits over the prior art. The rejection was maintained in the Final Office Action.

(7) GROUPING OF CLAIMS

Group I: Claims 1-3 stand or fall independently.
Group II: Claims 6-8, 10, and 11 stand or fall independently.

(8) ARGUMENT

OBVIOUSNESS

In the previous appeal, the Board designated the rejection of Claims 1-3, 6-8, 10 and 11 under 35 USC 103(a) over Yamamoto ('906) and Nagpal ('279) in combination as a new ground of rejection. The Board has affirmed that Examiner has successfully made a prima facie case of obviousness.

In response to the new ground of rejection, the claims were amended to specify that the methods relate to "an effective amount of tazarotene and an effective amount of a high-potency corticosteroid". Applicant believes the specification of the present application contains evidence of unexpected results which are sufficient to overcome the obviousness rejection for the scope of the claims as currently amended, notwithstanding any prima facie obviousness that Examiner and the Board allege exists.

Referring to Example 1, and the accompanying Figure 2, it is clear that the combination of tazarotene and a high potency corticosteroid are surprisingly more efficacious than the other combinations tested, having a clear improvement over the other combinations virtually from the onset of the administration until reaching an advantage of about 15% over the next best treatment from 4 days until the end of the study. The Board stated that "the combination and tazarotene and a low-potency corticosteroid appear to provide better results than the combination of tazarotene and a mid-potency corticosteroid in reducing the severity of psoriasis in patients over a period of 12 weeks." The Board also observed "it appears that the combination of low-potency corticosteroid and tazarotene provides better results than the combination of mid-potency corticosteroid and tazarotene". According to the Board's observations, increasing the potency of the

corticosteroid has no apparent advantage in combinations up to mid-potency corticosteroids, thus it is surprising that the combination of tazarotene and a high-potency corticosteroid should have such a significant improvement over the other treatments. Figure 1 also shows a clinically significant reduction in plaque elevation for the tazarotene/high-potency corticosteroid combination compared to the other treatments. Thus, the combination of tazarotene and a high-potency corticosteroid represents a subset which has enhanced efficacy relative to the larger group represented by the combination of tazarotene and a corticosteroid, which enhanced efficacy would not be predicted based upon the properties of the remaining part of the larger group. This is the very essence of unexpected results.

The Board has alleged that "it is impossible to conclude from Table II that the incidence of adverse events was consistently lower in patients treated with mid- or high-potency corticosteroid in combination with tazarotene as compared with patients treated with low potency-corticosteroid in combination with tazarotene, or tazarotene alone." While Applicant does not agree with this assertion, he submits that this assertion is not valid for the claims as they now stand. According to Table II, the adverse events associated with the tazarotene/high-potency corticosteroid combination is at least as low or lower, than the other combinations with the exception of burning. Furthermore, the trend in the total number of adverse events points to a significant advantage for the tazarotene/high-potency corticosteroid combination. Consider that the table below, which gives the total number of adverse events for each treatment taken from Table II, clearly shows a trend for reduced frequency of adverse events with higher-potency corticosteroids used in combination with tazarotene.

	Patients (%)			
	Taz/plac	Taz/low	Taz/med	Taz/high
Total Adverse Events	41	39	31	26

For additional support of this position, Applicant submitted a reference by Gollnick (British Journal of Dermatology 1999; 140 (Suppl. 54): 18-23), published after the effective filing date of the present application, which is therefore not prior art, which

supports Applicant's assertion that high potency corticosteroids in combination with tazarotene have fewer side effects. The reference states "there was a trend towards a ***lower incidence of treatment-related adverse events as corticosteroid potency increased*** (from 42% with tazarotene plus placebo to 36%, 32%, and 31% with tazarotene plus the low-, mid-, and high potency corticosteroid, respectively)." The combination of the results presented in the present application and the teachings of the cited reference provide sufficient support for our conclusion that the presently claimed compositions have fewer side effects. (In fact, Applicant believes that this reference supports the assertion of unexpected results originally made in the application, and supports a broader claim scope than that being sought herein. Applicant is currently seeking the broader scope in a Continuing application.)

In response to the Applicant's showing of unexpected results Examiner has alleged that "in order to argue unexpected and/or unobvious results, the amount of corticosteroid in each case has to be kept constant." Applicant respectfully responds that this is incorrect, but that comparison is properly made using potency. A person of ordinary skill in the art recognizes that a therapeutically effective concentration of a drug varies from compound to compound. Thus comparison of a concentration of one compound to a concentration of a different compound is not proper. In fact, this position is inconsistent with the position taken earlier by the Board that "it appears that the combination of low-potency corticosteroid and tazarotene provides better results than the combination of mid-potency corticosteroid and tazarotene". This statement carries the implication that the effectiveness of a composition is directly related to the potency of the steroid, and that a person of ordinary skill will expect that a higher potency formulation of a corticosteroid, regardless of the concentration, is generally more effective than one of a lower potency. If two different drugs of the same concentration are expected to have similar activity, as Examiner seems to believe, the fact that the concentration of medium potency corticosteroid has a 20-fold lower concentration (0.05%) than the low potency corticosteroid (1%), but has similar activity, would surely be considered to be an unexpected result. As will further demonstrated with details to be presented later herein, the data is properly evaluated considering the potency of the corticosteroid formulations.

Furthermore, Examiner's position is inconsistent with itself in that Examiner alleges "[t]he skilled artisan would have the reasonable expectation that the higher concentration of betamethasone valerate would result in better improvement over treatment with lower concencentration of alcometasone dipropionate" but fails to recognize that the same reasoning would lead a skilled artisan to expect that the lower concentrations of alcometasone dipropionate and betamethasone valerate relative to hydrocortisone acetate would result in the treatment by the former two compounds being less effective. If the former two treatments are expected to be less effective, then the significant improvement of betamethasone valerate over hydrocortisone acetate that was observed must be unexpected. Thus, by Examiner's line of reasoning, a person of ordinary skill in the art would expect betamethasone valerate to be both more effective and less effective than hydrocortisone acetate. Any position which relies upon a line of reasoning that can yield contradictory conclusions, without support or clarification of the apparent contradiction, is inherently flawed.

Those skilled in the art, recognizing that the concentration of different compounds with different properties cannot be used to predict the therapeutic activity of a composition, have devised a potency scale to apply to corticosteroids. Generally, the potency of a corticosteroid is based upon the performance of said steroid in a vasoconstriction assay. ***The potency of the corticosteroid is assigned according to the particular formulation in which it is contained.*** Thus, the 1% hydrocortisone acetate formulation used in the patent specification is considered to be low-potency at a concentration of 1% in the vehicle it is administered. The same is true for 0.05% alcometasone dipropionate being a medium-potency corticosteroid and 0.1% betamethasone valerate being a high-potency corticosteroid. The whole point of assigning potency to a corticosteroid ***formulation*** is to indicate the activity of that ***formulation***, and thus treatment for a particular condition is determined according to the assigned potencies of the various corticosteroid ***formulations***. It is known in the art that corticosteroid formulation potency correlates very well with efficacy in the treatment of psoriasis. For example, Cornell and Stoughton carried out a study to determine the correlation between a vasoconstrictor assay (a test for potency) and the clinical activity in

psoriasis (Arch Dermatol vol 121, Jan 1985, pp. 63-67. An excerpt from the abstract is reproduced below:

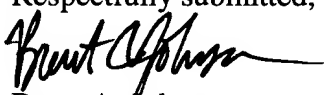
> Excellent correlation between the vasoconstriction assay and selected paired comparison studies occurred in 20 of 23 instances...vasoconstrictor assay is an inexpensive and reliable method for screening glucocorticosteroid ***formulations*** for clinical activity in psoriasis.

Based upon this evidence and the other arguments presented herein, Applicant believes that the Examiner's position with regard to concentration is irrelevant. Therefore, the Examiner has failed to provide any evidence or reasoning that the unexpected results cited herein relevant to potency are insufficient to show nonobviousness of the claimed combination.

The Advisory Action indicated that "request for reconsideration has been considered but does NOT place the application in condition for allowance because: of the reasons of record". However, in the request for reconsideration, Applicant presented arguments and evidence similar to those presented above related to concentration and potency, and no response was given to justify the erroneous argument presented in the Final Office Action.

In view of the above, the Board is asked to reverse the Examiner's holding of all of the pending claims as unpatentable and direct the Examiner to pass the claims to issue.

Respectfully submitted,



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CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. §1.10

I hereby certify that this Brief on Appeal Brief, in triplicate, and the documents referred to as enclosed herein are being deposited with the United States Postal Service on **MARCH 26, 2004** in an envelope as "Express Mail Post Office To Addressee" mailing label number **EV193720985US** with sufficient postage for Express Mail addressed to Mail Stop Appeal Brief - Patents, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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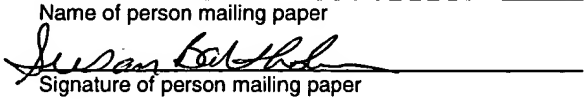
Name of person mailing paper



Signature of person mailing paper

Date: March 26, 2004

(7) APPENDIX

CLAIMS

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a high-potency corticosteroid.

2. The method of claim 1 wherein said corticosteroid is selected from the group consisting of mometasone furoate, fluocinonide, and betamethasone valerate.

3. The method of claim 1 wherein tazarotene is applied as a 0.1% gel.

4. Cancelled.

5. Cancelled.

6. A method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a high-potency corticosteroid.

7. The method of claim 6 wherein tazarotene is applied as a 0.1% gel.

8. The method of claim 7 wherein said corticosteroid is a cream.

9. Cancelled.

10. The method of claim 6 wherein said corticosteroid is selected from the group consisting of mometasone furoate and fluocinonide.

11. The method of claim 11 wherein tazarotene is administered once daily in the evening and the corticosteroid is administered once daily in the morning.

12. Cancelled.

13. Cancelled.

British Journal of Dermatology 1999; **140** (Suppl. 54): 18–23.

Combination therapy with tazarotene plus a topical corticosteroid for the treatment of plaque psoriasis

H.GOLLNICK AND A.MENTER*

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Summary Although tazarotene monotherapy is generally efficacious and well tolerated, studies show that both the efficacy and the tolerability of tazarotene therapy can be further improved when it is used in combination with certain topical corticosteroids. The studies reported here evaluate the usefulness of two potential combination regimens. In one regimen, a corticosteroid is added to tazarotene treatment. In the other regimen, corticosteroid treatment alternates on a daily basis with tazarotene treatment. The results of the first study, which involved 300 patients, showed that additive combination therapy using tazarotene plus a mid- or high-potency topical corticosteroid significantly increased the percentage of plaques achieving treatment success at the end of the treatment period, compared with tazarotene plus placebo (91% and 95% vs. 80%, respectively; $P<0{\cdot}05$ for both). Similarly, tazarotene plus a mid- or high-potency topical corticosteroid reduced the incidence of patient withdrawals compared with tazarotene plus placebo (5·5% and 9·6% vs. 13·3%). The results of the second study, which involved 398 patients, showed that a combination regimen that alternates between tazarotene and a high-potency topical corticosteroid treatment each day, significantly increased the treatment success rate compared with regimens using tazarotene alternating with a mid-potency corticosteroid or placebo (75% vs. 55% and 54%, respectively, at the end of the treatment period; $P<0{\cdot}05$ for both). In addition, there was a trend towards a lower incidence of treatment-related adverse events as corticosteroid potency increased (from 42% with tazarotene plus placebo to 36%, 32%, and 31% with tazarotene plus the low-, mid-, and high-potency corticosteroid, respectively). Both treatment regimens are potentially useful and offer a rational approach to optimizing the efficacy and tolerability of tazarotene treatment for plaque psoriasis.

Key words: combination, corticosteroid, psoriasis, tazarotene, topical.

Introduction

The main therapeutic options for the treatment of patients with stable plaque psoriasis include emollients, keratolytic agents, tar preparations, corticosteroids, topical or oral retinoids, vitamin D analogues, anthralin, and phototherapy. Each treatment has its relative advantages and disadvantages and, as in other areas of clinical medicine, various combinations of these treatments have been investigated in an attempt to improve the overall efficacy, tolerability, and acceptability of therapy.[1] Rotational therapy has also been used to maximize efficacy and minimize the risk of adverse events.[2–4] In such therapy, patients are switched between different monotherapies or combination therapies according to the stage and type of psoriasis and the patient's individual needs.

Topical treatments are the most widely used therapy in patients with mild-to-moderate psoriasis because only a limited area of their skin is affected and the use of systemic therapies, with their attendant problems, is not warranted. In the U.S.A., corticosteroids have tended to be the most widely used of the topical agents[5] because of their relatively good efficacy, tolerability, cosmetic acceptability, and cost. The prolonged use of topical steroids, however, can be associated with resistance and a rebound effect on withdrawal of treatment.[6] The early topical retinoids that were available before the approval of tazarotene were generally found to have only limited efficacy or to induce intolerable skin irritation.[7–10] Because tazarotene is selective for RAR-γ and RAR-β receptors, it has a more targeted action on psoriatic keratinocytes compared with older

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retinoids and helps prevent stimulation of those retinoid pathways that are apparently unrelated to the pathophysiology of psoriasis. This is likely to promote both good efficacy and good tolerability.

Combination therapy with tazarotene and a topical corticosteroid appears logical because these agents have some different (as well as some common) mechanisms of action, and thus are likely to have additive or synergistic effects. Although the exact mechanism of action of tazarotene remains to be fully elucidated, it is known to induce the expression of at least three so-called 'tazarotene-induced genes' (TIGs).[11–13] Our understanding of the role of the proteins expressed by these genes is limited, but the product of TIG-1 is believed to function as a cellular adhesion molecule to promote better cell–cell contact and reduce keratinocyte proliferation,[11] and the product of TIG-2 may be a soluble ligand for cell surface receptors.[12] TIG-3 may be involved in tumour suppression.[13] Whatever the precise mechanism of action of tazarotene, studies suggest that it helps correct three of the major pathogenic features of psoriasis: keratinocyte hyperproliferation (Allergan Inc., data on file), abnormal keratinocyte differentiation,[14] and infiltration of inflammatory components.[14]

Corticosteroids also have anti-proliferative and anti-inflammatory properties and, in addition, have immunosuppressive effects.[15] In contrast to tazarotene, the mechanism of action of corticosteroids is thought to be mediated through the induction of phospholipase A_2 inhibitory proteins, which inhibit the synthesis of various cytokines.[16] The antigen-induced release of such cytokines is thought to contribute to the inflammation associated with psoriasis,[17] and such a mechanism of action would therefore explain the anti-inflammatory actions of corticosteroids.

Previous studies have shown the relative advantages of retinoids and corticosteroids. The addition of a non-receptor-selective topical retinoid to corticosteroid therapy has been shown to at least partially ameliorate corticosteroid-induced epidermal atrophy.[18,19] Similarly, treatment with tazarotene, the first receptor-selective topical retinoid, has been observed to reverse some of the skin atrophy induced by superpotent corticosteroid therapy (Dr Prystowsky, personal communication), and also to be associated with a lower cumulative probability of relapse 12 weeks post-treatment compared with corticosteroid therapy.[20] Advantages of corticosteroids include their ability to improve the efficacy of retinoic acid therapy[10] and to reduce the incidence of retinoic acid-induced skin irritation.[8]

It is timely to perform further investigations into potential therapeutic regimens utilizing both tazarotene and topical corticosteroids. The results of two large, multicentre studies that evaluated two such potential regimens are reported here. The first study evaluated the clinical benefits of adding a low-potency, mid-potency, or high-potency topical corticosteroid to tazarotene therapy. The second study utilized a combination regimen that switched between tazarotene therapy and topical corticosteroid therapy every day. Although rotational therapy using dithranol, D_3-derivatives, corticosteroids, and/or ultraviolet light as monotherapy or combination therapy is well known,[1–4,21,22] the concept of an alternate-day regimen of corticosteroids with other topical drugs remains relatively unexplored. It is somewhat surprising that such alternate-day regimens have not been more widely investigated.

Subjects and methods

Additive combination of tazarotene plus corticosteroid

A multicentre, investigator-masked, parallel-group study was performed in order to investigate the efficacy and tolerability of combination tazarotene and topical corticosteroid treatment.[23] All patients were at least 21 years of age and had stable plaque psoriasis on no more than 20% of their body surface area (BSA). Patients were randomized to receive tazarotene 0·1% gel once daily in the evening plus one of the following once daily in the morning: low-potency corticosteroid cream (0·01% fluocinolone acetonide), mid-potency corticosteroid cream (0·1% mometasone furoate), high-potency corticosteroid cream (0·05% fluocinonide), or placebo (vehicle) cream. The treatment period was 12 weeks in duration and patients were followed for an additional 4 weeks after treatment had ended.

Comparisons among the four treatment groups were performed by the two-way ANOVA model. If among-group differences were significant (overall F-test at $P \leq 0{\cdot}05$), between-group comparisons were performed by means of Fisher's protected least significant differences test.[24]

Alternating between tazarotene and corticosteroid each day

A multicentre, double-blind, parallel-group study was performed to evaluate the efficacy, tolerability, and acceptability of alternate-day treatment with tazarotene gel and a corticosteroid cream. All patients were at least 21 years of age and had stable plaque psoriasis on no more than 20% of their BSA. Patients were randomized

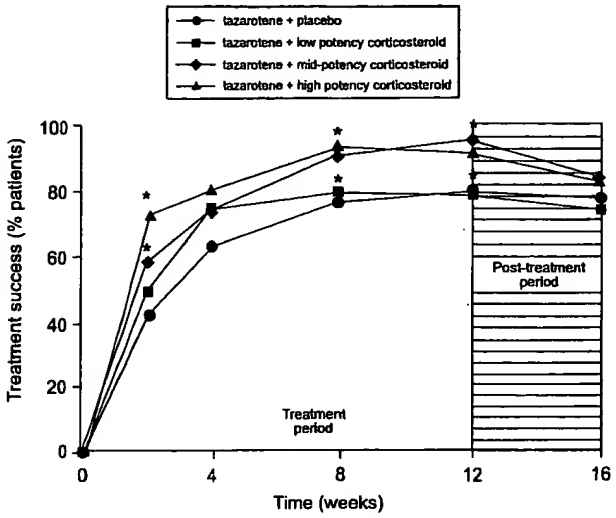


Figure 1. Percentage of patients achieving treatment success (≥ 50% global improvement in psoriasis) during treatment with tazarotene 0·1% gel plus placebo or a low-, mid-, or high-potency topical corticosteroid, both given once daily for 12 weeks.

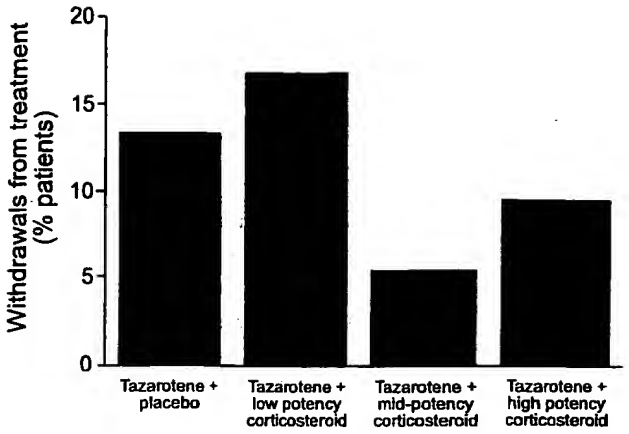


Figure 2. The incidence of patients withdrawing from treatment with tazarotene 0·1% gel plus placebo or a topical corticosteroid (low, medium or high potency), both given once daily for 12 weeks.

to receive tazarotene 0·1% gel every other evening for 12 weeks and, on the intervening evenings, to receive one of four creams: placebo, low-potency corticosteroid (1% hydrocortisone acetate), medium-potency corticosteroid (0·05% alclometasone dipropionate), or high-potency corticosteroid (0·1% betamethasone valerate; classified as a mid-potency steroid in the U.S.A.). The 12-week treatment period was followed by a 4-week follow-up period.

Primary efficacy variables were the global response to treatment and the degree of plaque elevation. A 7-point scale was used to assess the global response to treatment (completely cleared, almost cleared, marked response, moderate response, slight response, condition unchanged, condition worsened). Treatment success was again defined as ≥ 50% global clinical improvement in psoriasis.

Secondary efficacy variables included the degree of scaling and the degree of erythema. A 9-point grading scale was used to assess the degree of plaque elevation, scaling, and erythema (grade 0 = none; 2 = mild; 4 = moderate; 6 = severe; and 8 = very severe, with 1, 3, 5, and 7 serving as mid-points). A 2-point reduction on this scale was considered clinically significant. Superiority was defined as a statistically significant difference between treatments ($P \leq 0{\cdot}05$).

Baseline and changes from baseline at each subsequent visit were analysed using the extended Cochran–Mantel–Haenszel test for ordinal data stratified by country[25] employing modified ridit scores.[26,27] Within-group comparisons to baseline at each follow-up visit were performed by the Wilcoxon signed-rank test. Pair-wise between-group comparisons were considered significant only if the overall Cochran–Mantel–Haenszel test was significant.

Results

Additive combination of tazarotene plus corticosteroid

A total of 300 patients were enrolled from centres across the USA and Canada.

Treatment success. Treatment success was defined as ≥ 50% global improvement in the appearance of the lesions. Treatment success rates were consistently higher in patients treated with tazarotene plus the mid- or high-potency corticosteroid (taz/mid and taz/high, respectively), compared with those treated with tazarotene plus placebo or the low-potency corticosteroid (taz/plac and taz/low, respectively) (Fig. 1). Treatment success rates with taz/mid and taz/high were significantly higher than taz/plac at Weeks 2, 8, and 12 of treatment. At Week 12, treatment success rates were 91% with taz/mid and 95% with taz/high, compared with 80% with taz/plac ($P < 0{\cdot}05$ for both). Plaques treated with taz/mid or taz/high also reached initial treatment success significantly faster than plaques treated with taz/plac (a median time of 2 and 3 weeks, respectively, compared with 4 weeks).

Plaque elevation, scaling, and erythema. All treatment groups experienced significant reductions in plaque elevation, scaling, and erythema from baseline

values. There were no significant between-group differences in the degree of plaque elevation, but the degree of scaling was consistently and significantly lower in the plaques treated with taz/mid or taz/high than in the taz/plac group throughout the treatment period. At Week 4, erythema was significantly lower in the groups receiving tazarotene plus the higher potency corticosteroids than in both of the other groups.

Adverse events. Local skin reactions (burning, pruritus, and erythema), typically associated with topical retinoid therapy, were the most common adverse events that occurred in the study. There was a trend towards a lower incidence of treatment-related adverse events in patients receiving mid- and high-potency corticosteroids compared with those receiving the placebo or low-potency corticosteroid (for example, 4·2% and 11·4% of patients experienced burning vs. 14·5% and 18·1% after 2 weeks, respectively). There was also a lower incidence of patient withdrawals in the groups receiving mid-potency (5·5%) or high-potency corticosteroids (9·6%), compared with the groups receiving placebo (13·3%) or low-potency corticosteroid (16·7%) (Fig. 2). As patient withdrawal rates can be an indication of the severity of adverse events, they are perhaps a truer reflection of the clinical importance of adverse events than the incidence rates of adverse events alone are.

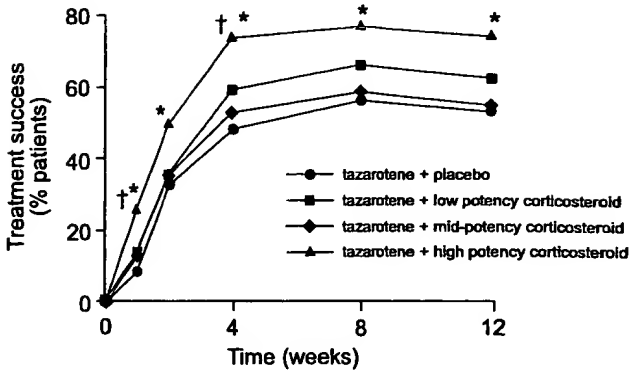
Alternating between tazarotene and corticosteroid each day

A total of 398 patients, of which 388 were evaluable for efficacy, were enrolled in the study from 41 centres across France, Germany, and The Netherlands.

Treatment success. Although all treatment groups achieved treatment success rates of >50% within 8 weeks, the most efficacious treatment was clearly the taz/high combination (Fig. 3). This treatment achieved significantly greater treatment success rates than the taz/plac and taz/mid combinations throughout the 12-week treatment period ($P<0·05$). The taz/high combination also achieved significantly greater treatment success rates than the taz/low combination at weeks 1 and 4 ($P<0·05$).

In addition, the taz/high combination achieved initial treatment success significantly faster than any of the other combinations. The median time to initial treatment success was 2 weeks in the taz/high group, compared with 4 weeks in each of the other groups.

Of the 368 patients who completed 12 weeks' treatment, 210 (57·1%) patients returned for the post-treatment visit. In this subgroup of patients, the treatment success rate was ≥ 60% in each treatment group. There were no significant between-group differences.



* $P < 0.05$ vs tazarotene + placebo and tazarotene + mid-potency corticostroid;
† $P < 0.05$ vs tazarotene + low potency corticosteroid

Figure 3. Percentage of patients achieving treatment success (≥ 50% global improvement in psoriasis) when treated for 12 weeks with tazarotene 0·1% gel every other day plus placebo or a low-, mid-, or high-potency topical corticosteroid on the intervening days.

Plaque elevation. All treatment groups achieved statistically significant reductions in plaque elevation from baseline during the study, with the taz/high group achieving consistently greater reductions than the other treatments throughout the treatment period. At week 4, these reductions were significantly greater than those in all the other treatment groups ($P<0·05$). The taz/high combination also achieved clinically significant reductions in plaque elevation more rapidly than the other treatments—in 2 weeks, compared with 4 weeks in all the other groups. Generally, the reductions in plaque elevation achieved by week 12 did not vary markedly during the ensuing 4-week follow-up period.

Scaling. As with the results for plaque elevation, all treatment groups achieved statistically significant reductions in scaling from baseline during the treatment period. At week 4, the reductions in scaling were significantly greater in the plaques treated with taz/high than in the plaques treated with taz/plac or taz/mid ($P<0·05$). The reductions in scaling achieved in all groups by the end of the treatment period remained largely unchanged during the 4-week follow-up period.

Erythema. All treatment groups achieved statistically significant reductions in erythema from baseline during the treatment period (taz/plac from week 2 onwards).

The tazarotene plus high-potency corticosteroid combination was the most efficacious treatment, achieving significantly greater reductions in erythema than any of the other treatments at weeks 4 and 8 ($P<0·05$), and clinically significant improvements in erythema at weeks 8 and 12.

During the follow-up period there were no significant between-group differences. All groups retained statistically significant reductions in erythema compared with baseline levels.

Adverse events. The majority of adverse events in all four treatment groups were mild to moderate in severity, and consisted predominantly of local irritation, including pruritus, erythema, and burning skin. The incidence of treatment-related adverse events decreased with increased corticosteroid potency, falling from 42% in the taz/plac group, to 36%, 32%, and then 31% in the taz/low, taz/mid, and taz/high groups, respectively. There were no statistically significant differences in the incidence of adverse events between treatment groups, and no clinically meaningful increases in the incidence of treatment-related adverse events over the 12-week treatment period. The incidence of discontinuations due to adverse events was 14–16% in all groups, with no apparent between-group differences.

Twelve patients experienced serious adverse events (taz/plac, three patients; taz/low, one; taz/mid, five; taz/high, three), but all such events were judged unrelated to the study treatment.

Discussion

Tazarotene has previously been shown to offer improved tolerability compared with non-selective retinoids. Both studies reported here demonstrate that utilizing a topical corticosteroid cream in combination with tazarotene can further improve both efficacy and tolerability compared with tazarotene plus placebo cream. The two therapies complement one another. The corticosteroid enhances efficacy and ameliorates the perilesional irritation that may arise with topical retinoids such as tazarotene. Furthermore, the efficacy of tazarotene allows the dose of corticosteroid to be minimized, thus lowering the potential for corticosteroid-induced adverse events such as epidermal atrophy.

In the studies reported here, the benefits of using a mid- or high-potency corticosteroid in an *additive* combination regimen with tazarotene, compared with tazarotene plus placebo, included significant improvements in several measures of efficacy—higher rates of treatment success, faster achievement of initial treatment success, a lower degree of scaling, and a transiently lower degree of erythema. The benefits of using a high-potency corticosteroid in an *alternating* combination regimen with tazarotene included significantly higher rates of treatment success and significantly faster achievement of initial treatment success. Whereas the benefits of the additive regimen were achievable with either the mid-potency or the high-potency corticosteroid, the benefits of the alternating regimen were predominantly associated with the use of the high-potency corticosteroid (betamethasone valerate). However, as the potency ranking of corticosteroids differs between countries (betamethasone valerate 0·1% is classified as a high-potency steroid in Europe and a mid-potency steroid in the U.S.A.), it is difficult to generalize about specific potency issues.

In both studies, one group of patients was treated with tazarotene plus vehicle cream (rather than tazarotene alone) in order to control any potential influence from the cream base of the steroids as well as to replicate good clinical practice. (In addition, we recommend the use of emollients in order to help maximize the efficacy and tolerability of tazarotene monotherapy.) In clinical practice, if patients are not using emollients, then the efficacy and tolerability benefits of adding a corticosteroid to tazarotene treatment are likely to be even more pronounced than indicated in these studies.

In countries that currently do not favour the use of topical corticosteroids to treat plaque psoriasis, the results of these studies are likely to lead to a revival in the use of corticosteroids and thus a change in the therapeutic armamentarium. It is logical to treat chronic plaque psoriasis with two agents that have additive or synergistic effects and further research is now required to determine the optimal dose regimen for combination therapy utilizing tazarotene and a corticosteroid. In clinical practice, in order to minimize the risk of steroid rebound and other steroid-induced adverse effects, it may be advisable to slowly wean patients off the steroid after the initial 3–4 weeks as the clinical effect from tazarotene starts to become apparent, and then to continue treatment with tazarotene monotherapy (non-atrophogenic mid-potency corticosteroids such as methyprednisone-aceponat or prednicarbet).

The addition of a mid- or high-potency topical corticosteroid to tazarotene therapy offers a valuable means of optimizing the efficacy and tolerability of treatment for plaque psoriasis. Both the additive and the alternating regimens reported here appear to

offer significant clinical advantages over tazarotene monotherapy.

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